Exhibit 1

Research paper

Effect of drug type on the degradation rate of PLGA matrices

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Abstract

We compare the rate of drug release through the degradation of 50:50 polylactic-co-glycolic acid polymer pellets, for six different drugs: Thiothixene, Haloperidol, Hydrochlorothiozide, Corticosterone, Ibuprofen, and Aspirin. Despite using the same polymer matrix and drug loading (20% by weight), we find that the rate of polymer degradation and the drug release profile differ significantly between the drugs. We conclude that the design of biodegradable polymeric drug carriers with high drug loadings must account for the effect of the drug on the polymer degradation and drug release rate.
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1. Introduction

Patient non-compliance with medication regimes may lead to relapses and re-hospitalizations. Yet, a significant fraction of patients find it difficult to adhere to a prescribed medication program over even moderate periods of time [1–5]. Controlled release of drugs from biodegradable polymer matrices promises to reduce patient non-compliance, and has been widely investigated as a tool for the long-term release of drugs [6,7]. While decanoate preparation [3,4] or conjugation [8,9] require chemical modification of the drugs, degradable polymer delivery agents rely on mechanical mixing of the drug into the polymeric matrix. As a result, such delivery agents may be used in the delivery of a wide variety of drugs and therapeutic agents.

The utilization of any long-term drug delivery system requires exact control of the dosage released as a function of time. High release rates can lead to toxic drug levels, while low ones may be below the efficacy threshold. Thus, understanding the processes governing degradation and drug release, in vitro and in vivo is essential.

The effect of polymer properties on the rate of drug release from biodegradable polymeric matrices has been widely studied (see, for example, [10–16]). Recent studies have found, however, that the type of drug also plays a role in setting the release rate [17,18]. Frank et al. [17] compare the release of base and salt forms of lidocaine from several degradable polymers, finding that the chemistry of the drug affects both the rate of matrix degradation and the rate of water absorption into the matrix. Kiortsis et al. [18] have shown that the drug solubility affects the swelling and release rate from cellulosic polymers.

In this paper, we examine the release rate of six different drugs from a biodegradable polymeric matrix. The polymeric matrix used, polylactide co-glycolide (PLGA), is a highly biocompatible, mechanically processable polymer that degrades to water soluble, non-toxic products of normal metabolism [10–12] through hydrolysis. PLGA has been examined as a matrix for long-term delivery of a

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variety of drugs [10–12,19–24], and its properties are well understood. The drugs used in the study include Thiothixene, Haloperidol, Hydrochlorothiozide, Corticosterone, Ibuprofen, and Aspirin (see Table 1).

2. Materials and methods

2.1. Drugs

Six drugs were examined. Their properties are listed in Table 1.

N,N-Dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]thioxanthene-2-sulfonamid (Thiothixene)

4-[4-(4-Chlorophenyl)-4-hydroxy-1-piperidyl]-1-(4-fluorophenyl)-butan-1-one (Haloperidol)

9-Chloro-5,5-dioxo-5$|^2$$\{6\}$-thia-2,4-diazabicyclo[4.4.0]deca-6,8,10-triene-8-sulfonamide (Hydrochlorothiozide, HCTZ)

11-Hydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydrocyclopenta[a]phenanthren-3-one (Corticosterone)

2-[4-(2-Methylpropyl)phenyl]propanoic acid (Ibuprofen)

2-Acetyloxybenzoic acid (Aspirin)

Their properties are listed in Table 1. All drugs were obtained from Sigma–Aldrich, Inc.

2.2. Polymer

The polymer used in all studies was 50:50 PLGA, 63 kDa, from Alkermes. The polymer intrinsic viscosity is 0.38–0.48 dL/g (as measured by Alkermes), where our own measurements show 0.44 dL/g.

2.3. Ultraviolet (UV) scanning

Each drug was dissolved in a phosphate-buffered saline solution to expected in vitro levels. Using ultraviolet cuvettes, an absorbance scan was performed on each drug solution within the range of 200–400 nm. A blank cuvette containing only the saline solution was used as a reference cell. A characteristic ultraviolet footprint was generated for

each of the drugs examined to determine the wavelength at which the relevant maximum peak occurred, for use later in in vitro assays. Standard curves were prepared for each drug in the phosphate-buffered saline solution so that absorbancies could be converted to concentrations using the Lambert–Bear law. For all drugs, it was determined that no polymer (or polymer degradation product) was found at the drug absorbance, thereby rendering the methodology quantitative.

The characteristic UV absorbance XXX of each drug are listed in Table 1.

2.4. Polymer/drug pellet fabrication

Four hundred milligrams of 50:50 polylactic-glycolic acid biodegradable polymer (Alkermes, Inc.) and 100 mg of a given drug were solvent cast to give a 20% by mass drug-load. The polymer and drug were dissolved in 45 mL acetone (Fisher Scientific, Inc.) and vortexed. The mixture was poured into an evaporation dish and placed in a vacuum oven at 40 °C under 3 in-Hg vacuum with trace airflow. After seven days, the dishes were removed from the oven. The evaporation residue was a thin film mixture of polymer and drug with homogenous in appearance. The film was carefully weighed to confirm complete removal of solvent and pressed into disk shaped pellets to yield final dimensions of 6 ± 0.15 mm wide, 1.2 ± 0.3 mm thick. The Teflon®-coated pellet press was set at 25 klb and heated to 60 °C. This procedure was repeated for each drug, yielding four uniform polymer pellets for each drug–polymer mixture. The resulting pellets were carefully weighed and dimensions were measured to compare the densities of each pellet. Negative control pellets with a 0% drug load were fabricated in the same manner, with the exception that 500 mg polymer – and no drug – used in the solvent casting.

2.5. Drug solubility in water

Ascending mass of drug, ranging from 0.5 to 200 mg, of each drug was mixed into a capped glass jar (Wheaton, Inc.) containing 10–50 mL of distilled water. The jars were

Table 1
Drug properties and parameters of the drug release profile

Drug	Molecular formula	Molecular weight	UV abs. peak (nm)	Water solubility (mg/mL)[a]	OH group density[b]	Maximal release[d] (days)	St.St release[e]
Haloperidol	$C_{21}H_{23}ClFNO_2$	375.87	249	0.13	2.66×10^{-3}	38	0.029 ± 0.001
Thiothixene	$C_{23}H_{29}N_3O_2S_2$	443.64	227	0.14 ± 0.1	0	16	0.07 ± 0.001
HCTZ[c]	$C_7H_8ClN_3O_4S_2$	297.75	271	2.00 ± 1.00	0	25	$0.0074 \pm 0.001, 0.11 \pm 0.001$
Corticosterone[c]	$C_{21}H_{30}O_4$	346.47	247	0.50	5.77×10^{-3}	25	$0.0048 \pm 0.001, 0.12 \pm 0.001$
Ibuprofen	$C_{13}H_{18}O_2$	206.29	225	0.47	4.85×10^{-3}	27	0.044 ± 0.015
Aspirin	$C_9H_8O_4$	180.16	296	4.99	5.55×10^{-3}	13	0.095 ± 0.001

[a] Measured after 14 days using the method described in the text. Measurement error is ± 0.01 mg/mL unless stated otherwise.

[b] Number of OH groups/unit mass.

[c] These drugs are characterized by two steady-state release rates: a slow one initially, and a rapid one at later times (see Fig. 3).

[d] As measured by $f = 1$ from Fig. 2a.

[e] As measured by $\Delta f/\Delta t$ from Fig. 2a, in the steady-state regime. Units are 1/days.

stored in the dark, at 21 °C, with moderate mixing for 14 days. Aliquots of 1 mL of supernatant were taken from each jar at fixed time intervals and analyzed by UV spectroscopy to determine maximum saturation concentration for each drug.

2.6. In vitro assay

From each set of four uniform pellets, three were chosen so that the assays could be performed in triplicate. Each polymer–drug pellet was added to a separate amber-glass, capped jar (Wheaton, Inc.) containing 500 mL of a phosphate-buffered saline solution with pH 7.4. The jars were stored in the dark, at 37 °C, with moderate shaking. Aliquots of 1 mL were taken from each jar at fixed time intervals and analyzed by UV spectroscopy. Positive control jars consisted of 500 mL phosphate-buffered saline and 10 mg of given drug, the expected maximum release for a 20% drug-loaded pellet with a mass of 50 mg. These controls were also aliquotted frequently to check the stability of each drug in saline solution over the experimental periods of time. As may be expected, all drugs were stable over the experiment time period.

3. Results and discussion

In Fig. 1 we show pictures of pellets containing the six different drugs, and a control (pure polymer, without any drug) taken at given intervals over a period of 21 days. For brevity we will refer in the following to polymer pellets containing a given drug by the drug name; thus, a PLGA pellet containing Aspirin will be referred to as 'Aspirin pellet'.

At day 0 we see that all pellets are identical, as expected from our preparation method. However, by day 7 differences develop: Aspirin and Thiothixene clearly show some degree of swelling (se seen by irregular edges to the pellet), while the other drugs and the control seem largely unchanged. Thiothixene pellets disintegrate between days 7 and 14, while the control and the aspirin undergo disintegration in the interval between day 14 and 21. By day 21 the control, Aspirin and Thiothixene are fragmented, Hydrochlorothiozide and Ibuprofen display a small 'core' surrounded by what seems like a swollen 'corona'. Corticosterone is largely unchanged, while haloperidol is smaller but circular in shape. Thus, the rate of matrix degradation depends on the drug type. Thiothixene accelerates the degradation of the polymer pellet, when compared to a drug-free control, while HCTZ, Ibuprofen, Corticosterone and Haloperidol slow the degradation process. Quite surprisingly, Aspirin does not significantly affect the degradation rate when compared to the control (see Fig. 1), despite the fact that the Aspirin products in water (Acetic acid and Salicylic acid) may be expected to increase the local pH, thus changing the PLGA hydrolysis rate [10–12,21–24].
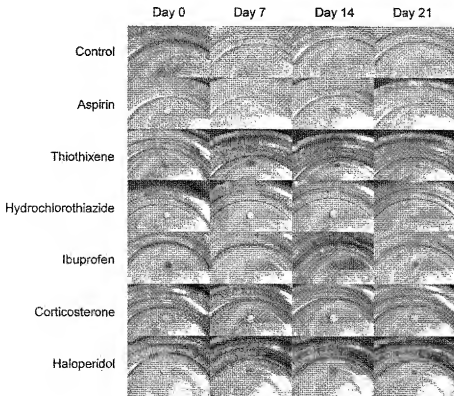

Fig. 1. Time evolution of the drug-containing polymer pellets. Pictures were taken, for all six drugs, at constant intervals. The location of the camera was the same in all cases. Ruler scale is cm/mm. We see that although all pellets start at day 0 the same size and shape, over time differences evolve, as discussed in the text.

Our results are in agreement with the recent observations of Li et al. [19], who found that the presence of a drug (caffeine) in PLA matrices affected the rate of degradation.

Degradable polymers undergo degradation via two routes: Surface erosion takes place at the interface between the polymer and the suspension, and is characteristic of systems where the diffusion of reactants (i.e. water in our system) into the matrix is suppressed. Bulk erosion occurs when the rate of diffusion into the matrix is rapid when compared to the degradation reaction kinetics. As shown in Fig. 2, the degree of pellet swelling or shrinkage is drug dependent: only Aspirin degrades in a somewhat similar manner to that of the control (drug-free) pellet, although the profile is somewhat different. However, the change in pellet diameter in HCTZ and Haloperidol containing pellets, as a function of time, is significantly different. Aspirin containing pellets swell rapidly, a signature of bulk erosion (in agreement with Fig. 1). On the other hand, the diameter of Haloperidol containing pellets remains more or less constant for a period of time, followed by a steady decrease in size, consistent with surface erosion. Thus, we may conclude that the drugs affect both the rate and the mechanism of polymer degradation.

Drug release from a degrading matrix is not necessarily correlated to the rate of polymer degradation. For example, drug may diffuse, or leach, out of a non-degrading matrix. Therefore, to quantify the drug release profile we measure, directly, the amount of released drug as a function of time using UV.
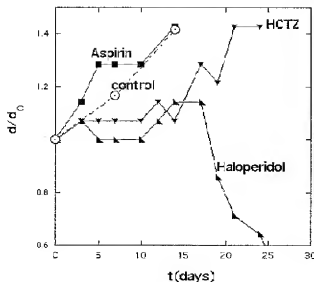
In Fig. 3 we plot the amount of drug released (given in f, the fraction of the overall amount of drug in the pellet) as a function of time. We find, for all drugs, a classic S release profile and an absence of sharp peaks that may indicate 'bursts'. The lack of drug release bursts suggests that the drug mixing in the pellets is relatively uniform: for example, the formation of a drug coating on the pellet surface, which is quite common in drug delivery systems, would be evident by a high release rate initially. Similarly, the lack of release spikes indicates that there are no regions with large drug crystals. It is possible, however, that small crystals may have formed, so that the drug is not molecularly mixed with the polymer.

We see that the different drugs display different release profiles, as characterized by two parameters: The time required for maximal release (namely, to achieve $f = 1$) and the steady-state release rate (the slope $\Delta f/\Delta t$). These are listed in Table 1: The time for full release varies between 13 and 38 days, while the steady-state release rate varies over an order of magnitude. Also, comparison with Fig. 1 shows that, indeed, degradation is not the only mechanism for drug release. For example, visual observation of Corticosterone does not show significant degradation or swelling up to day 21, yet the quantitative release profile shows the onset of a rapid release rate from day 15, culminating in complete release by day 25.

To determine the effect of the drug characteristics on the release rate we must correlate the release parameters to some drug property. One might expect that, since the polymer degradation is achieved via hydrolysis, the rate of degradation would be set by the chemistry of the drug,
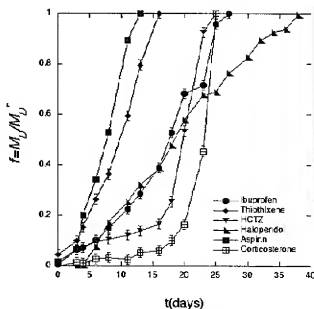

Fig. 2. Time evolution of the pellet diameter d (normalized by the initial diameter d_0) for three drugs, as compared to the control (drug free) pellet. We see that the degradation behavior of HCTZ and Haloperidol significantly differs from that of the drug-free polymer. Even in the case of Aspirin, where the overall degradation rate is similar to that of the control, the profile of degradation is quite different. Aspirin displays rapid swelling, HCTZ a slower swelling rate, and Haloperidol undergoes a time period where the diameter remains relatively constant, followed by a slow reduction in diameter.

Fig. 3. The fraction of drug released (f) as a function of time, for all six drugs, as measured by UV. Note that, since all pellets contained the same weight fraction (20%) of drug, f is equivalent to the mass of released drug. We see that the drugs differ in the overall time for 100% release (namely, the time required for $f = 1$), the rate of drug release (the slope), and whether the release is conducted in a single or a double regime.

specifically the presence of OH groups and/or the pH of the water-dissolution products. Yet, as shown in Table 1, there seems to be no correlation between the density of OH groups and the drug release parameters.

Kiortsis et al. [18] have shown that the % release of drugs from cellulosic polymers, at a fixed time point, depends on the drug solubility in water; it seems reasonable that hydrophilic drugs with high solubility may increase the rate of water diffusion into the matrix, thereby accelerating release and (bulk) erosion, while highly hydrophobic drugs with low solubility will inhibit water diffusion into the matrix, thereby slowing the release rate and inducing surface erosion. In Fig. 4a we plot the fraction of drug released by day 3 and day 8 (taken from the data of Fig. 3), as a function of the drug solubility, as measured under the same conditions as the dissolution experiments. We see that there is no direct correlation; After 3 days, the fraction of released drug seems to generally increase with solubility (with one exception, Thiothixene). However, on day 8 it seems like the fraction release varies non-monotonically with solubility, with a *minimum* at solubility values of ~0.5 mg/ml.

The fraction released, or the time required for 100% release ($f = 1$) is a parameter that depends on the pellet formulation, shape and so on. The steady-state rate of release, as determined by the amount of drug released per unit time, may be a more general measure of the release rate. In Fig. 4b we plot the slope as a function of drug solubility. We see that, although the general trend may be that of increasing slope with increasing solubility, the correlation is weak at best. (Note that for the drugs that display two regimes, HCTZ and Corticosterone, we used the initial, or low, slope value, as given in Table 1. Using the higher slope value did not yield a better relationship than that displayed in Fig. 4b).

As discussed above, drug release may take place as the result of two processes: Drug diffusion and leaching out of the matrix, and matrix degradation. In the case of the Corticosterone and HCTZ drug diffusion seems to be a significant component (see Fig. 1 vs 3); however, can we

correlate the rate of drug release to degradation in the other four systems?

In the case of PLGA, degradation takes place via hydrolysis. Thus, polymer degradation is determined by the rate of water diffusion into the pellet (swelling) and the hydrolysis reaction rate. To evaluate the effect of the drugs on the water diffusion rate into the pellet and the effective reaction rate we adapt a reaction/diffusion model that has been suggested for PLGA degradation [25–33] to estimate the changes in the water diffusion coefficient and the effective hydrolysis rate due to the drug incorporation. The details of the model are given in the Appendix A. The model fit to the four drugs matches the entire release profile, despite the differences in the steady-state release rate and the maximal time for release.

The effective diffusion coefficient of water into the matrix, and the effective hydrolysis rate obtained from the model fit are listed in Table 2. We see that, as may be expected, both the diffusion (swelling) rate and degradation rate are highest for Aspirin, the most hydrophilic drug. Also as expected are the low diffusion and reaction values for Haloperidol, which is a relatively hydrophobic drug with low solubility. However, the results for Thiothixene and Ibuprofen are less clear, and are likely to require a more detailed understanding of the relationship between these molecules and water than that expressed by solubility.

Table 2
Fit coefficients of the diffusion/reaction model

Drug	Water solubility (mg/mL)[a]	OH group density[b]	D^b	k^b
Haloperidol	0.13	2.66×10^{-3}	8×10^{-5}	1.5×10^{-5}
Thiothixene	0.14 ± 0.1	0	0.0015	0.002
Ibuprofen	0.47	4.85×10^{-3}	0.0004	0.01
Aspirin	4.99	5.55×10^{-3}	0.0046	0.059

[a] Effective rate of water diffusion into the pellet, as determined from fitting the release rate profile to the model equation (5).
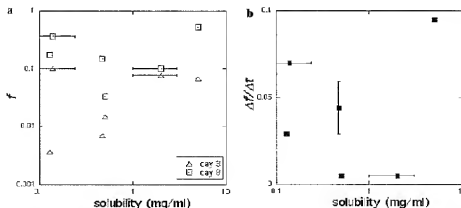[b] Effective rate of polymer degradation reaction, determined from the model fit (Eq. 5) to the release profile.

Fig. 4. The effect of drug solubility in water on the drug release parameters. (a) The fraction of drug released after 3 days ($\triangle$) and 8 days ($\square$). (b) The steady-state slope, as determined from Fig. 3. We see that there is only a weak correlation, at best, between the solubility and any of the release parameters.

4. Conclusions

The ability to accurately control the rate of drug release from biodegradable polymeric matrices is essential for the utilization of these systems in therapeutic applications. In this paper we investigate the process of degradation and drug release from 50:50 PLGA pellets containing 20% (weight) drug, for several common drugs. We find that the mechanism of pellet degradation and the parameters of the drug release rate vary as a function of the drug type. The presence of the drug may change the degradation mechanism from bulk erosion (control) to surface degradation (Haloperidol), as well as affect the rate of pellet degradation. The drug release profile, as defined by the time required for 100% release and the steady-state rate also varies significantly. The drug release profile for four of the drugs seems to follow classic diffusion/reaction kinetics. However, efforts to correlate the release rate parameters to the drug chemistry (as defined by the density of OH groups) or hydrophilicity (as given by solubility in water) did not yield a strong relationship. Thus, we conclude that drug incorporation affects the rate of polymer degradation and release rate significantly, but further study is needed to determine the relationship between the drug properties and the release rate.

Appendix A.

Here we adapt the reaction/diffusion approach [24,29] to obtain a simple, analytical expression for the rate of drug release that can capture either bulk or surface erosion. For simplicity we assume that the mobility (diffusion) of the drug in the polymeric matrix is negligible compared to the polymer degradation rate.

PLGA degradation into lactic acid and glycolic acid (water soluble, non-toxic products of normal metabolism [10–12,19–23]) occurs through a reaction with water. Thus, the rate of degradation depends on the availability of water molecules. In systems where the diffusion of water into the pellet is suppressed, this indicates surface erosion. In systems where the diffusivity of water into the polymer is high, this leads to bulk erosion.

The degradation reaction is taken, for simplicity, to be a 1st order reaction between the polymer and water [24–33], and is thus proportional to the local concentration of both species. However, since the polymer comprises the majority of the pellet, we assume that its concentration is fixed everywhere. Thus, the degradation reaction is proportional to the local concentration of water (a function of the diffu-

sivity) times a constant. Defining the diffusion coefficient of water into the polymer pellet as D, we may write the diffusion/reaction equation for water as [25,26]

$$\frac{\partial c_w}{\partial t} = D\nabla^2 c_w - kc_w \qquad (1)$$

where k is the reaction rate (which includes the local polymer concentration, taken to be constant). Appropriate boundary conditions are that the concentration of water at the particle edge is fixed by the solution value c_w^0, and that initially (at $t = 0$) the concentration of water in the particle is zero.

Eq. (1) indicates that in systems where $D \to 0$ there is no diffusion into the polymeric particle, c_w is zero within the pellet, and all reactions take place at the polymer/solution interface. In systems where the diffusion rate is large (when compared to the reaction rate) water will penetrate- and degrade- the entire particle volume through bulk erosion. We solve for the water concentration profile by assuming that the pellet is a semi-infinite medium. This assumption is appropriate for the initial and steady-state stages of the degradation when the diffusion distance of the water is small compared to pellet dimensions, but will break down at later stages.

Defining the distance from the polymer/solution interface as x we find [25]

$$\frac{c_w}{c_w^0} = e^{-kt}\left(1 - \text{erf}\left[\frac{x}{\sqrt{Dt}}\right]\right)$$
$$+ k\int_0^t e^{-kt'}\left(1 - \text{erf}\left[\frac{x}{\sqrt{Dt'}}\right]\right)dt' \qquad (2)$$

The amount of polymer that reacted, at any given location (x), with water and degraded is then obtained through integration over time

$$dM_p(x,t) = k\int_0^t c_w(x,t')\,dt' \qquad (3.a)$$

where $dM_p(x,t)$ is the change in polymer pellet mass at point x. Thus, the overall mass of degraded polymer is given by

$$\Delta M_p = \int_{x=0}^{\infty} dM_p(x,t)\,dx = k\int_{x=0}^{\infty}\int_0^t c_w(x,t')\,dt'\,dx \qquad (3.b)$$

and the amount of released drug M_d (neglecting drug diffusion) is

$$M_d(t) = \phi dM_p = \phi k\int_0^{\infty}\int_0^t c_w(x,t')\,dt'\,dx \qquad (4)$$

where ϕ is the weight fraction of the drug in the particle. Initially, when t is small, M_d is given by

$$M_d = \frac{\phi c_w^0}{4}\sqrt{\frac{D}{\pi k^3}}\left(2e^{-kt}\sqrt{kt} + \sqrt{\pi}[2kt-1]\,\text{erf}\left[\sqrt{kt}\right]\right) \qquad (5)$$

Note that M_d is in units of drug released *per unit surface area*. In the limit of long times (steady state), the release rate is given by $\phi c_w^0 t\sqrt{D/2k}$, while initially it is equal to $2\phi c_w^0 t^{3/2}\sqrt{D/9\pi}$.

Initially, the amount of drug released increases with time to the power of (3/2), with a release rate (the slope) that is determined only by the water diffusion coefficient D. As time increases, the amount of released drug becomes linear with time. In this regime the system reaches 'steady state' where the degradation rate, and the amount of drug released, are constant with time. In this limit the release rate (slope) varies as the ratio between the diffusion and reaction constants. Note that the model does not account for the finite size of the implant [28], namely, the end-tail of the steady-state release period.

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